Original Research Article

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Effect of combined therapy of oral levamisole with topical doxycycline in management of oral lichen planus - A Clinical Trial"

Abstract:

Background: Oral lichen planus (OLP) is a chronic, mucosal inflammatory disease with a probable immune mediated etiopathogenesis. There are multiple treatment modalities in which corticosteroids are the most commonly used drugs to manage OLP. To minimize the adverse effects of steroid therapy, steroid-sparing agents have gained popularity in the management of OLP. Levamisole and doxycycline are two pharmacological agents with anti-inflammatory, immunomodulating properties which can be considered for treatment of oral lichen planus.

Aim: To evaluate the effect of combined therapy of oral levamisole with topical doxycycline in management of oral lichen planus.

Method: 20 clinically and histopathologically diagnosed, symptomatic OLP patients were administered 50mg of oral levamisole with topical application of 5% doxycycline for three months. Signs, symptoms, and subjective treatment scores were evaluated at baseline and 3 months.Lesion recurrence was checked 3 months post completion of therapy.

Results: Statistically significant reduction in signs and symptoms scores was seen with the administered regimen. A recurrence of 15% was seen post completion of therapy which was statistically insignificant.

Conclusion: Dual therapy of oral levamisole with topical doxycycline is a feasible and effective treatment regimen in management of OLP with minimal recurrence rate.

Key-words: Combined Therapy, Levamisole, Oral lichen planus, topical doxycycline.

Introduction:

Lichen planus (LP) is a chronic, T-cell mediated, inflammatory disease affecting dermis and mucous membrane, showing periods of relapse and remission. Oral LP (OLP) is its mucosal counterpart occurring with or without dermal manifestation, affecting 0.5-2% of all racial groups with reported Indian prevalence of 0.69-2.6%.[1–5] Many theories on etiopathogenesis have been proposed in OLP, among which immunological aberrations have been identified to play a significant role in development and prognosis.[6]

Usually reticular OLP is asymptomatic, kept under non interventional clinical observation. Whereas management of symptomatic OLP includes use of high-potency topical or systemic corticosteroids.[7] However, this may predispose the patient for opportunistic infection such as oral candidiasis especially in comorbidities like diabetes mellitus (DM), hypertension (HTN) and malignancy.[8,9] There is an upsurge in successful management of OLP with steroid sparing agents.

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Levamisole is a broad spectrum anti-helminthic, immunomodulatory agent used in several malignancies, tumor remission, and autoimmune diseases.[9,10] It restores phagocytic activity of macrophages and neutrophils, potentiate human interferon, and modulate T-cell mediated immunity, making it a potential candidate for OLP management.[9] Concomitantly, doxycycline is a semi-synthetic tetracycline with higher anti-inflammatory activity compared to other tetracyclines due to its TNF-α, interleukin (IL)-1β, 6, and 8 suppression activities.[11] It also possess anti-collagenase, prostaglandin and leukocyte suppression, and matrix metalloproteinase collagenase downregulation properties making it a potential adjuvant for OLP however, lacks adequate literature evidence.[12]

Showing lack of spontaneous remission with malignant transformation rate of 0.5-2%, OLP is a lesion of concern constantly demanding newer treatment regimens.[3,9,13] Thus, the following study was undertaken to assess the role of levamisole with concomitant use of topical 5% doxycycline in the management of symptomatic OLP.

Aim:

To assess and compare signs and symptoms of OLP before and after combined therapy of levamisole and topical doxycycline.

Methodology:

The clinical assessments were done in the department of oral medicine and radiology, Government Dental College and Research Institute, Bangalore, Karnataka, India, respectively between December 2013 to September 2015 after obtaining approval from the institutional ethics committee. Consecutive patients were enrolled based on the set criteria (table 1) and a signed informed consent was obtained in their vernacular language.

Table 1: Inclusion and exclusion criteria for patients

Inclusion criteria	Exclusion criteria
• Patients between 18-60 years of age with no gender bias. • Clinically symptomatic and histologically diagnosed OLP. • Patients not taking any treatment for OLP since two weeks.	• Patients having hepatitis, any other autoimmune diseases, drug allergies,systemic diseases like DM, HTN, HIV. • Patients under systemic steroids, anti-coagulants, or immune suppressive therapy. • Pregnant or lactating women.

After obtaining detailed case history, a thorough clinical and oral examination was performed to give a clinical diagnosis of symptomatic OLP using Thongprasom's criteria (Table 2) and were subjected to incisional biopsy under local anesthesia.[8] Histopathological diagnosis of OLP was confirmed based on World Health Organization's (WHO) diagnostic criteria. Staging of initial symptoms with subjective evaluation for need of treatment was done using Tel Aviv-San Francisco Scale (TASF) (Table 3).[14]

Table 2: Thongprasom criteria for clinical scoring[8]

Score	Oral Examination
5	White striae with erosive area > 1 cm^2
4	White striae with erosive area < 1 cm^2
3	White striae with atrophic area > 1 cm^2
2	White striae with atrophic area < 1 cm^2
1	Mild white striae, no erythematous area
0	No lesion, normal mucosa

Legend: >: More than, <: Less than

Table 3: Tel Aviv-San Francisco scale for Staging of initial symptoms and subjective treatment

Stage	Symptoms	Stage	Subjective Evaluation
100	Asymptomatic	4	90%-100% remission of signs and symptoms
75	Low level of symptoms; does not interfere with usual daily activity	3	70%-80% benefit; treatment not required
50	Symptoms interfere with regular daily activity	2	50% benefits
25	Sore andpainful; greatly interferes with regular daily activity	1	30%-50% improvement; treatment still needed
0	Impossible to live with this severity of symptoms	0	Little improvement or no change
		-1	Deterioration or regression

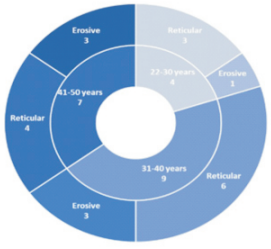
Patch test was done to rule out hypersensitivity reaction to drugs. 50mg oral levamisole was administered thrice daily after food for three days once a week per month for three months. simultaneously, pharmacist prepared 5% topical doxycycline hyclate in orabase was administered twice daily after food for three months. Clinical and subjective assessments were done before and after completion of therapy. Patients were advised to report in case of worsening of symptoms or with any adverse effects. Three months post completion of treatment, patients were followed up to six months .

Descriptive and inferential statistics were done using SPSS version 21.0. Mean difference and correlations were calculated using paired t-test and Pearson correlation, respectively. Results are presented as mean ± standard deviation (SD) and percentages, as applicable. The level of significance was kept at p-value <0.05.

Results:

20 patients (6 males, 14 females) were enrolled having mean age of 37.05 ± 9.78 years with most patients between 31-40 years of age (figure 1).

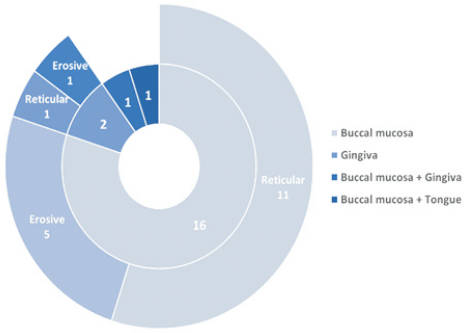
Figure 1: Distribution of patients according to age group and type of oral lichen planus



All patients had either reticular or erosive LP involving buccal

mucosa, gingiva, or tongue. Multiple sites involvement was seen in 2 patients (figure 2).

Figure 2: Distribution of patients according to site of involvement



Mean pre-treatment symptom score of 46.25 ± 21.88 was seen in all patients with lower scores seen in erosive OLP with higher frequency (table 4).

Table 4: Pre-treatment symptom score based of type and site of oral lichen planus

Type of OLP	Number of Patients	Pre-Treatment Symptom Score	Number of Patients	Site of OLP	Number of Patients	p-value
Reticular	13	25	2	Buccal	1	<0.001
				Gingiva	1	
		50	5	Buccal	4	
				Gingiva	0	
				Buccal + Gingiva	1	
		75	6	Buccal	6	
				Gingiva	0	
Erosive	7	25	7	Buccal	5	
				Gingiva	1	
				Buccal + Tongue	1	
		50	0	Buccal	0	
				Gingiva	0	
		75	0	Buccal	0	
				Gingiva	0	

Legend:OLP: Oral Lichen Planus

Reticular OLP patients had sign scores in the range of 2-4 while erosive OLP patients had range of 2-5. Maximum patients had a score of 3 (7 reticular and 3 erosive OLP patients), showing no statistically significant difference between the two groups (p-value = 0.095).

Post-treatment symptom and sign scores:

Among reticular OLP patients, 8 and 5 patients had maximum symptom score of 100 and 75, respectively while all 7 patients of erosive OLP had symptom score of 75 showing a statistically significant difference (p-value <0.001).

Post-treatment, 11 out of 13 reticular OLP patients had maximum sign score value of 1 while remaining had sign score value of 2. Among 7 erosive OLP patients, maximum sign score value of 2 was seen in 4 patients, with score of 3 and 1 found in 2 and 1 patient, respectively, presenting a statistically non-significant difference (p-value = 0.158).

Significance between pre- and post-treatment symptom and sign scores

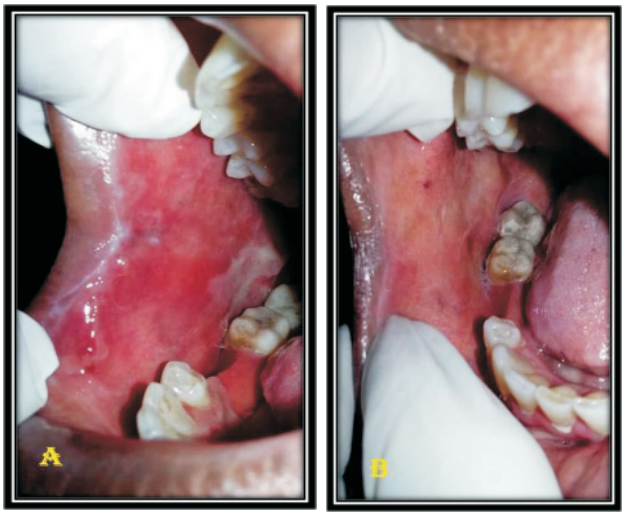
Highly statistically significant decrease and increase in post-treatment symptom and sign scores, respectively was seen for complete sample (p-value <0.0001). Individually, similar trend was seen for reticular OLP cases (p-value <0.0002). Erosive OLP showed statistically significant increase in sign scores (p-value < 0.001) while variation in symptom scores could not computed (table 5& figure 3).

Table 5: Pre-and Post-treatment Comparison of Variables

Type of OLP	Variable	Posttreatment (a) (Mean±SD)	Pre-treatment (b) (Mean±SD)	Mean Difference (a – b)	SD	p-value
Complete Sample	Symptom score	85.00 ± 12.57	46.25 ± 21.88	38.75	15.12	0.000**
	Sign score	1.50 ± 0.688	3.25 ± 0.91	-1.75	0.55	0.000**
Reticular OLP	Symptom score	90.38 ± 12.66	57.69 ± 18.78	32.69	15.76	0.0001*
	Sign score	1.15 ± 0.38	3.00 ± 0.71	-1.85	0.56	0.000**
Erosive OLP	Symptom score	75.00 ± 00.00	25.00 ± 0.00	#	#	#
	Sign score	2.14 ± 0.69	3.71 ± 1.11	-1.57	0.53	0.000**

Legend: OLP: Oral lichen planus, **SD:** Standard deviation, **CI:** Confidence interval, ****:** Highly significant, ***:** Significant, **#:** Could not be calculated due to no difference in individual scores at the given points of time

Figure 3: Erosive Oral Lichen Planus Buccal Mucosa
A- Before treatment
B-After treatment



Recurrence rate and adverse effect:

Six months post completion of therapy, recurrence was seen in 3 patients (15%) among which 1 had reticular while 2 had erosive OLP. During treatment, 15% patients (3/20) reported adverse effects in form of nausea, vomiting, and stomach pain of which 2 had reticular (15.38%) and 1 had erosive OLP (14.29%).

Discussion:

Immunological etiopathogenesis of OLP makes its management and treatment monitoring a clinical challenge.

Various scoring scales for OLP have been proposed among which Thongprosom's is one of the oldest and most widely used as it evaluates presence of erythema, white striae, and atrophy, thus making it a comprehensive scoring tool.[15] Levamisole positively modifies T-cell mediated immunity and as a mono and combination therapy it has also shown promising results however, drug regime remains an enigma.[9,16] At the same time, topical doxycycline has been used to a limited potential due to non-available commercial preparations. A three-month treatment duration in the current study was opted for due to the chronic nature of the lesion and was in line with other studies undertaking long treatment durations.[17]

This study comprised of 20 symptomatic OLP patients showing a female predominance of 2.3:1, in line with reported epidemiology of approximately 1.61 however, some studies have reported otherwise.[1,3,18] This predominance can possibly be due to stress and altered hormone levels seen with higher frequency in females, predisposing them to OLP development. Most diagnosed patients were in the third decade of life having mean age of 37.05 ± 9.78 years which was lower than reported ages in regions like central China, Spain, UK, and Italy thus indicating the possible role of ethnic and geographical variations. Buccal mucosa was the most involved anatomical site (80%) followed by gingiva and tongue. This varied a little from other observations which reports buccal mucosa, tongue, gingiva, lower lip, palate, and floor of mouth involvement in sequence.[4,18] All cases in this study were either reticular or erosive in nature which are reported to the most common clinical presentations having refractory and severe symptoms.[17]

TASF score and scorings by Thongprasom*et al* are the most comprehensive, feasible, and easy to follow, covering a wide range of symptoms, and were thus used in the current study. Most of the patients in our study had a mean symptom score of 50 and maximum sign score value of 3 before treatment, whereas these values changed to maximum symptom and sign scores of 100 and 1, respectively post-treatment. These results were similar to those of Pratibha *et al* who although did not see an initial response with levamisole therapy ultimately reported symptomatic relief after eight weeks of therapy.[17] Individually also, a significant statistical difference (p-value = 0.001) was noted in the symptom and sign scores for OLP subtypes. Subjective treatment evaluation showed 61.5% of reticular OLP patients to have 90-100% improvement while 15.4% patients had 70-80% relief. Comparatively, all erosive OLP patients had 70-80% relief in signs and symptoms. Similar observations have been reported with previous studies using levamisole and Chinese medicinal herbs.[9,17,19]

Our results can be explained based on therapeutic efficiency of levamisole which immunomodulates T-cell mediated and humoral immunities in OLP patients, restoring the normal phagocytic activity of macrophages and neutrophils. Levamisole also normalizes the decreased CD4+/CD8+ ratio and the reverses the aberrant cellular and humoral immunities which may explain the marked symptom improvement however, the ratio was not assessed in the current work. [20] The profound anti-inflammatory effect of topical doxycycline potentiates the action of levamisole thereby helping in early resolution of treatment.

15% of our patients reported side effects with levamisole which was statistically insignificant. A cyclic regimen of levamisole administration was followed for the purpose of reducing these side effects and avoiding the rarely seen severe side effect in the form of agranulocytosis.[17] Thus, it was concluded that the drug can be safely used for management of symptomatic OLP. Conclusive comparisons about recurrence rate could not be made due to lack of similar results in previous works however our study observed a low recurrence rate of 28.6% and 7.7% for erosive and reticular OLP, respectively six months after initiation of treatment.[16,19]

Small sample size with lack of control group in the current study highlights the need for future research as case-control, age, and gender matched study design with larger sample size. This will help in generating stronger scientific evidence for regular and confident use of oral levamisole and topical doxycycline that can be adopted in regular clinical practice for management of symptomatic OLP.

Conclusion:

This preliminary study found therapeutic regime of cyclic 50mg oral levamisole with topical 5% doxycycline for three months as a valuable treatment alternative for symptomatic OLP with insignificant adverse effects. Although statistically insignificant, recurrence rates of 7.7% and 28.6% in reticular and erosive OLP, respectively can be due to small sample size thus highlighting the need of further studies with larger sample size and longer follow up duration.

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